As a preliminary matter, Applicants enclose a second copy of a CRF in ASCII format which is identical to the paper copy of the Sequence Listing filed on February 3, 2000.

Applicants have amended pages 2 and 3 of the specification, as recommended by the Examiner, to delete duplicate subject matter contained on pages 4 to 5 of the specification.

I. The Claimed Invention Is Not Obvious

Claims 1-10 and 17-20 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Chen *et al.*, *Biochemistry*, **1997**, *36*, 11402-11407 (hereinafter, the "Chen" reference). Applicants traverse the rejection and respectfully request reconsideration thereof because the Chen reference neither teaches nor suggests Applicants' claimed inventions.

The Chen reference reports structure-based discovery of ligands that are targeted to double stranded RNA. In particular, The Chen reference reports that a series of lead compounds was generated through a database search for ligands with shape complementarity to the RNA deep major groove. The RNA molecule reported in the Chen reference is entirely complementary with itself, thus having a complete double helical structure with no regions of single stranded RNA. Of more than 400 compounds that were examined graphically and found to fit well into the deep major groove, only 11 compounds were selected for testing. In order to determine the binding site of one of the compounds, lividomycin, ^{19}F-NMR solvent isotope shift measurements were carried out on RNA duplexes containing 5-fluorouracil (FU) (see, page 11405, first column). The Chen reference teaches that when FU is incorporated into nucleic acid duplexes, the fluorine atom lies in the major groove providing a probe for binding interactions in that groove. The presence of a tightly bound ligand in the major groove should limit the solvent exposure of the major groove atoms and thereby decrease or eliminate the solvent isotope shift.

In contrast to the Chen reference, the molecular interaction sites recited in claims 1-5 and 17-20 are not limited to being comprised of a RNA double helix but, rather, can contain single stranded regions such as, for example, bulges and loops. There is no teaching or suggestion in the Chen reference that compounds which bind to secondary structures of RNA, other than the double helix, can be identified by any of the methods described therein or any other method. Indeed, the

single stranded regions of RNA do not comprise the deep major groove of the double helix. Thus, claims 1-5 and 17-20 are not obvious in view of the Chen reference. Further, Applicants have added new claims 21-25, which are directed to identifying ligands which bind to molecular interaction sites on mRNA, pre-mRNA, tRNA, rRNA, and snRNA. Significantly, each of these species of RNA comprises single stranded regions. Since the Chen reference does not teach or suggest identifying ligands which bind to molecular interaction sites on RNA molecules having single stranded regions, claims 21-25 are not obvious in view of the Chen reference.

Applicants have also added new claims 26-30, which are directed to identifying at least one molecular interaction site on the target RNA by comparing the nucleotide sequence of the target RNA with the nucleotide sequence of a RNA from a different taxonomic species, identifying at least one conserved region, and determining the secondary structure of the conserved region, support for which can be found at, for example, page 16, lines 19-25 of the specification. Nowhere does the Chen reference teach or suggest identifying the molecular interaction site in the manner required by Applicants' claims. Rather, the Chen reference provides a RNA double helix and simply desires to target a particular region, the deep major groove. Thus, new claims 26-30 are not obvious in view of the Chen reference.

Claims 4, 5, 9, 10, 24, 25, 29, and 30 require that the target RNA is contacted with a highly ranked member to form a complex, ionizing the complex, fragmenting the ionized complex, and determining whether the highly ranked member binds to the molecular interaction site. In contrast, the Chen reference reports that in order to determine the binding site, the RNA double helix is labeled with FU and ^{19}F-NMR solvent isotope shift measurements carried out. The claimed steps are clearly neither taught nor suggested in the Chen reference. Indeed, the Chen reference neither teaches nor suggests any alternative procedures. The Office Action mistakenly asserts that it would have been obvious to use mass spectrometry or NMR or X-ray crystallography to obtain structural information. The Office Action, however, points to nothing in the Chen reference or any other reference that would **"impel"** a modification of the disclosed methods of the Chen reference that would be necessary to arrive at the present invention. What the Office Action appears to suggest is that the claimed invention would have been obvious because it would have been possible to replace

the ^{19}F-NMR solvent isotope shift measurements with the steps recited in Applicants' claims. However, the mere possibility that the prior art can be modified does not itself provide the requisite motivation to do so. *In re Dien*, 152 U.S.P.Q. 550 (C.C.P.A. 1967) (incentive to seek improvement of existing process held to not render change made by applicant obvious, even where the change was one capable of being made from theoretical point of view). The mere possibility for modification and improvement is not the "motivating force" that the Patent Office Board of Appeals and the Federal Circuit have invariably required. If it were, then no modification would ever lack motivation since some change is always possible. It is only with the improper use of hindsight and with the benefit of the Applicants' disclosure that one can discern the desirability of the particular invention now claimed.

Further, it is not even clear, and the Office Action fails to establish, whether the methods of the Chen reference which are directed to determining the binding in the deep major groove of the RNA double helix can be replaced. A section 103 rejection based upon a modification of a reference that destroys the intent, purpose, or function of the invention disclosed in the reference is not proper and a *prima facie* case of obviousness cannot therefore be made. In short, there is no technological motivation for engaging in the modification of the Chen reference to encompass Applicants' claimed invention. See, *In re Gordon*, 733 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984) (to render the prior art inoperable for its intended purpose is the antithesis of obviousness). Thus, the statements in the Office Action in regard to the allegedly obvious replacement of NMR by mass spectrometry are simply unsupported conclusions. If the present rejection is maintained, Applicant requests that the Examiner provide an affidavit containing evidence substantiating the position taken. 37 C.F.R. § 1.104(d)(2).

In view of the foregoing arguments, Applicants respectfully request that the rejection of claims 1-5 and 17-20, and as may be applied to new claims 21-30, under 35 U.S.C. §103(a) be withdrawn.

II. The Claimed Inventions Are Enabled

Claims 1-10 and 17-20 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to provide an enabling disclosure. The Office Action recognizes that the specification is enabling for the application of the DOCK program for modeling the interactions of known molecules with a macromolecule's binding site, but asserts that the specification does not provide enablement for generally discovering the binding sites in macromolecules. Applicant traverses the rejection and respectfully requests reconsideration since one skilled in the art would not be required to perform any amount of undue experimentation to practice the claimed invention.

As will be recognized, the enablement requirement of § 112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under § 112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented ***must*** be taken as in compliance with the enabling requirements of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. (emphasis added)

Any assertion by the Patent Office that an enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so

expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974).

The Office Action mistakenly asserts that Applicants' specification does not enable one skilled in the art to discover the binding sites in macromolecules whose three dimensional structure has not been determined by X-ray or NMR methods and refers to page 62, lines 6-13 of Applicants' specification for support. To the extent that the Office Action doubts that Applicants can identify binding sites (molecular interaction sites) in macromolecules (target RNAs) whose three dimensional structure has not been determined by X-ray or NMR methods, Applicants direct the Examiner's attention to Example 1 of the specification beginning at page 131. Applicants teach that the iron responsive element (IRE) serves as an excellent example of how Applicants' methodology of identifying a molecular interaction site works. Applicants thoroughly teach one skilled in the art to use the human mRNA sequence for ferritin as the initial mRNA sequence, find related sequences in the database, identify conserved regions, and identify the secondary structure (see pages 131 to page 134). Significantly, none of these steps requires that the three-dimensional structure of the IRE be known. The secondary structure thus identified is a molecular interaction site, which can then be examined for the ability to bind members of a virtual library of compounds using, for example, the DOCK program. Applicants teach that a number of commercially available computer programs can be used to convert the molecular interaction site into a three-dimensional representation (see, for example, page 94, line 25 to page 96, line 15) . Although the three-dimensional structure of the IRE has, in fact, been determined by NMR, Applicants methods do not require or even make use of the three-dimensional NMR analysis information of IRE in identifying the molecular interaction site. Indeed, the fact that the three-dimensional structure of the IRE has been determined merely confirms that Applicants method of identifying a molecular interaction site works. Thus, in contrast to the assertions in the Office Action, Applicants methods of identifying at least one molecular interaction site within a target RNA do not require that the three-dimensional structure be previously determined by X-ray or NMR methods.

Further, Applicants submit that the portion of Applicants' specification referred to in the Office Action has been taken completely out of context. As stated on page 61, lines 28-32,

Applicants teach that the library members or compounds as well as the target molecules can be converted into three-dimensional representations. Applicants further teach at page 62 that a variety of theoretical and computational methods are known in the literature to study the interactions of small molecules with biological targets. Applicants then teach that, typically, these studies were performed when the structure of the protein receptor was known. The Office Action failed to consider the teachings of the Applicants recited in the specification immediately after the portion of the specification referred to in the Office Action. Indeed, Applicants teach that a significant advance was Applicants' realization that software programs, such as DOCK, could be used for structure-based database searches to find and identify the interactions of known molecules to a receptor of interest. DOCK allows the screening of molecules, whose three-dimensional structures have been generated *in silico*, but for which no prior knowledge of interactions with the receptor is available. Thus, once the three-dimensional structure of a particular target has been generated *in silico*, the DOCK program can be used to facilitate binding of the target molecule to a particular library compound *in silico*.

The Office Action also mistakenly asserts that if the molecular interaction sites are not exposed on the surface of the macromolecule, and are thus buried, none of the commercially available software can be used to discover them. The Office Action, however, has misconstrued Applicants' invention. Applicants' claimed invention is not directed to creating three-dimensional structures of macromolecules and then looking for molecular interaction sites within them. As stated above, a molecular interaction site is identified by, for example, finding sequences related to an initial RNA sequence, identifying conserved regions within both initial and related sequence(s), and identifying the secondary structure of the conserved region. Identification of a molecular interaction site is, thus, independent of where the molecular interaction site occurs within the macromolecule.

The Office Action also appears to assert that it would require undue experimentation to convert an RNA target to a three-dimensional representation. First, Applicants are not converting the RNA target to a three-dimensional representation but, rather, are converting the molecular interaction site to a three-dimensional representation. Second, Applicants teach many methods of designing molecules with three-dimensional representations (see, for example, page 94, line 25 to

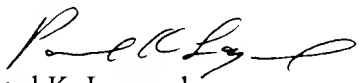
page 95, line 3 of the specification). Applicants teaching that a "Monte Carlo search procedure can sample the possible conformations of the RNA consistent with the program constraints and produce three dimensional structures" is but one way of producing three-dimensional representations. Third, the Office Action provides no evidentiary support for the conclusion that it would be impossible for one skilled in the art to use a Monte Carlo procedure to sample the conformations of RNA containing 2-3 dozens of base pairs. Finally, the fact that Applicants have DOCKed library members to a number of target RNAs (see, for example, Examples 8 and 9), renders the conclusory statement in the Office Action without merit. The Office Action further asserts that the optional structural refinement taught by Applicants at page 96, lines 1-2 of the specification cannot be performed on commercially available supercomputers. Aside from the fact that the Office Action offers no evidentiary support for the conclusory statement (and Applicants maintain that the Office Action is incorrect), Applicants point out that such steps are not required by the claims.

Applicants' specification fully enables one skilled in the art to make and use Applicants' claimed invention without being required to perform any amount of undue experimentation. Accordingly, Applicants respectfully request that the rejection of claims 1-5 and 17-20, and as may be applied to new claims 21-30, under 35 U.S.C. § 112, first paragraph be withdrawn.

III. Conclusion

In view of the foregoing, Applicant submits that the claims as amended are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Respectfully submitted,



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